REMARKS

Amendments to the Specification

Applicants respectfully request entry of the Amendments to the Specification set forth above to correct minor typographical errors. Specifically, paragraph 1 on page 2 is amended to correct the date of the citation from 1977 to 1997. Paragraph 1 on page 6 is amended to change "in" to "is". Paragraph 1 on page 10 replaces "straight-chair" and "branded-chair" with "straight-chain" and "branched-chair". Paragraph 2 on page 14 corrects "negatively charge group" to read "negatively charged group". Paragraph 2 on page 15 is amended to include the article "a" so that the amended phrase now states: "reflectance at a specified wavelength." Paragraph 1 on page 20 replaces "hemoglobin" with "albumin". Support for that amendment is found, for example, on page 20 ¶ 1. The second full paragraph on page 24 corrects the grammar of the sentence by changing "was" to "were". Paragraph 2 on page 25 amends pH=9 to read pH=9.5. Support for that amendment is found, for example, on page 25 ¶ 2.

Amendments to the Abstract

Applicants respectfully request entry of the Amendments to the Abstract set forth above. The amendment adds "protein" to the sentence, which otherwise does not make sense. This amendment to the abstract is consistent with the amendment to the claims discussed below and does not constitute new matter.

Amendments to Claims

Claims 1-34 have been cancelled. Claims 35-45 have been added. Support in the Specification for Claim 35 is found, for example, on page 13 ¶¶ 2, 3 and page 14 ¶ 1. Support for Claim 36 is found, for example, on page 14 ¶ 2. Support for Claim 37 is found, for example, on page 14 ¶ 2. Support for Claim 38 is found, for example, on page 14 ¶ 3. Support for Claim 39 is found, for example, on page 14 ¶ 3. Support for Claim 40 is found, for example, on page 16 ¶ 3. Support for Claim 41 is found, for example, on page 16 ¶ 3. Support for Claim 42 is found, for example, on page 16 ¶ 3. Support for Claim 43 is found, for example, on page 21 ¶¶ 2-4 and page 22 ¶¶ 1-2. Support for Claim 44 is found, for example, on page 15 ¶ 2; page 16 ¶ 3

and page 21 ¶ 2. Support for Claim 45 is found, for example, on page 19 ¶ 2. Support for Claim 46 is found, for example, on page 13 ¶¶ 2, 3; page 15 ¶ 3; and page 17 ¶ 3 and in Example 1. Support for Claim 47 is found, for example, on page 15 ¶ 4 - page 16 ¶ 1. Support for Claim 48 is found, for example, on page 15 ¶ 4 - page 16 ¶ 1 and page 18 ¶ 3.

Comments on Prior Office Actions

In prior Office Actions (October 6, 2004; April 19, 2005; August 10, 2005), the Examiner has cited Dean et al. (U.S. Pat. No. 4,269,605); Sanders (U.S. Pat. No. 4,407, 961) and May & Richards (GB 2206411 A). Although the above amendments to the claims are believed to be sufficient to address the Examiner's concerns, and clearly differentiate the claimed invention from the cited references, we nevertheless offer the following discussion of each of those references.

First, Dean et al. describes a different procedure for measuring a percentage of glycated hemoglobin than the procedure described in the instant application. The PTO can demonstrate inherency only if it shows that each step of the present claims is ***necessarily*** set forth in Dean et al. Instead, the PTO has apparently engaged in impermissible hindsight to find bits and pieces of disclosure in Dean et al. and combining them, arguing that this hindsight reconstruction would inherently anticipate the present method claims. This is directly contrary to binding precedent, as discussed in MPEP §2112, which states in relevant part:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) . . . ; *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) . . .
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

Thus, in order to make a *prima facie* inherency rejection, the PTO has the burden to point out a disclosure in the Dean reference of one particular set of method steps that are *identical* to those of the present claims, except for some undisclosed inherent properties or results. Those steps must *necessarily* result in the same properties or results specified in the present claims; probabilities or possibilities are not enough. *See* MPEP §2112. The PTO has failed to make out any case of inherent anticipation, since Dean does not teach the same method steps.

1. Dean does not teach binding both proteins, nor measuring total bound protein:

The present method claims require:

> binding *both* the glycated protein and the nonglycated protein to the negatively charged groups on the solid support at a first pH and *then performing a first measurement indicative of the amount of glycated and nonglycated forms of the protein bound to the solid support* (emphasis supplied).

Dean does not describe these steps at all. The entire focus of Dean is to differentially bind glycated protein to separate it from nonglycated protein. Dean nowhere discloses the selection of an appropriate pH for binding both glycated and non-glycated protein to negatively charged groups, or even that such binding can occur. Absent this affirmative teaching, Dean cannot anticipate or make obvious the present invention. In addition, Dean does not teach one to make the first claimed measurement, i.e., measuring the amount of bound glycated and nonglycated protein together. (The PTO points to Dean, Col. 5, line 37 for mention of percentage of total protein applied, but this is clearly in reference to "[d]etermination of recovered glycoprotein," i.e., after elution, so it does not refer to measuring bound protein, whether glycated or not.)

2. Dean does not teach a pH change after binding and measurement to remove only the nonglycated protein, nor a second measurement of bound protein

The PTO apparently argues that if Dean selects a cellulosic membrane from the laundry list of membranes in the patent, and if Dean selects a lower pH buffer, then both glycated and nonglycated protein would inherently be bound to the membrane and measured, despite the explicit statement in Col. 8, lines 10-11 that binding of non-glycosylated hemoglobin [is] negligible, and despite the statement that the lysed blood should be buffered to pH 7.5-9, preferably between pH 8 and 9 (Col. 6, lines 21-24, Col. 10. lines 26-31). However, even if this were true, and even if the "dipstick" embodiment cited by the PTO were made from a material

having negatively charged groups, and even if those groups were not all derivatized with a boryl group, there is at most **only one step disclosed in the reference in which bound protein is determined**; see, e.g., col. 6, line 7-10. This step is not a measurement, but a visual comparison against a color chart. (But for this visual evaluation of a dipstick, the whole focus of the reference relates to measuring eluted protein, not bound protein.)

In contrast, the present method claims require:

> *changing the pH on the support to the second pH* to remove both the nonglycated protein and the glycated protein from the negatively charged groups, whereupon the glycated protein immediately binds to the hydroxyboryl groups on the solid support without an incubation period, and *then performing a second measurement* indicative of the amount of the glycated protein bound to the solid support (emphasis supplied).

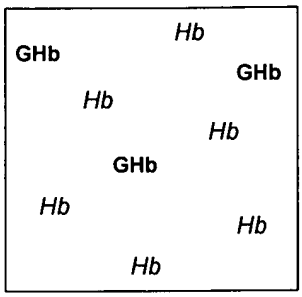
Dean further fails to anticipate because the reference does not teach changing the pH after the first measurement step to selectively remove nonglycated protein. Rinsing the membrane to remove nonglycated protein as disclosed in the reference does not meet this step, because that occurs before the any measurements are made, rather than after the first measurement as required in Claim 30. In short, even if both protein forms inherently bind in the Dean et al. reference, there is no disclosure whatsoever of the subsequent steps set forth above, including changing the pH to a second pH; selectively removing nonglycated protein; immediately re-binding glycated protein to hydroxyboryl groups, and performing a second measurement of *bound* glycated protein.

It is axiomatic that the reference should be considered as a whole, instead of picking and choosing isolated portions based on hindsight. Read as a whole, Dean et al. teaches that only the glycated hemoglobin is bound to boryl groups, Dean at col. 5 lines 60-62, and the non-glycated hemoglobin is rinsed off by a buffer solution, Dean at col. 5 lines 11-14, 63-65. The rinsed off hemoglobin is collected and then measured by absorbance, Dean at Example 1, col. 7 lines 21-24. The glycated hemoglobin is removed from the boryl groups, e.g., by washing with a buffer containing diol sugar (glucose, ribose, sorbitol), Dean at col. 5 lines 60-62; col. 6 lines 35-38; col. 7 lines 17-18. The sample is collected and measured by absorbance, Dean at col. 5 lines 35-39; col. 6 lines 15-16. The absorbance measurements are used to determine the percent of glycated hemoglobin in the sample, Dean at Example 1, col. 7 lines 21-32.

A visual comparison of the Dean et al. process and the process of the instant application (using hemoglobin as an example) is shown below:

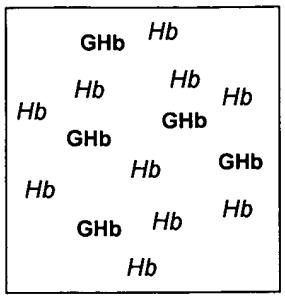
Dean et al.

1. **(DILUTED) BLOOD SAMPLE**

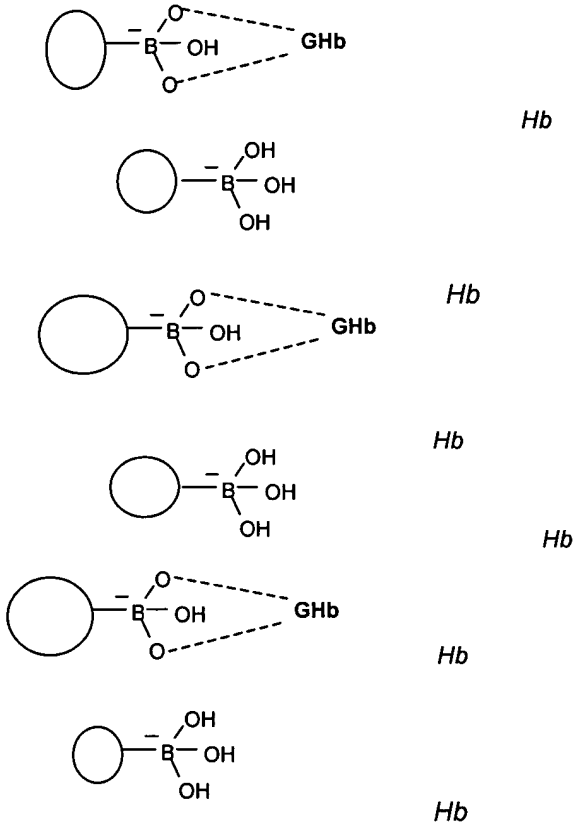


Present Application

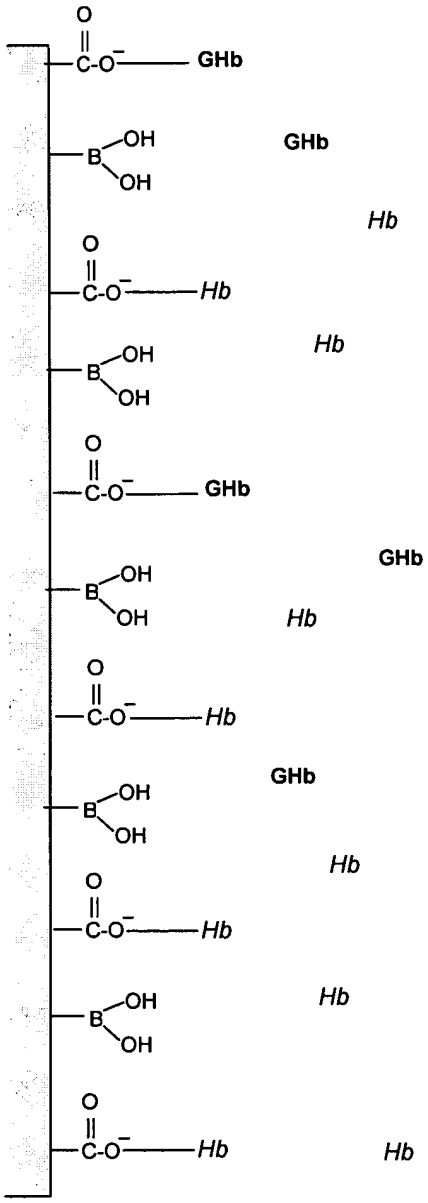
1. **BLOOD SAMPLE**



2. Add sample to solid support. Boronate groups bind glycated hemoglobin (GHb). High pH is best. (Col. 10, lines 25-31.)

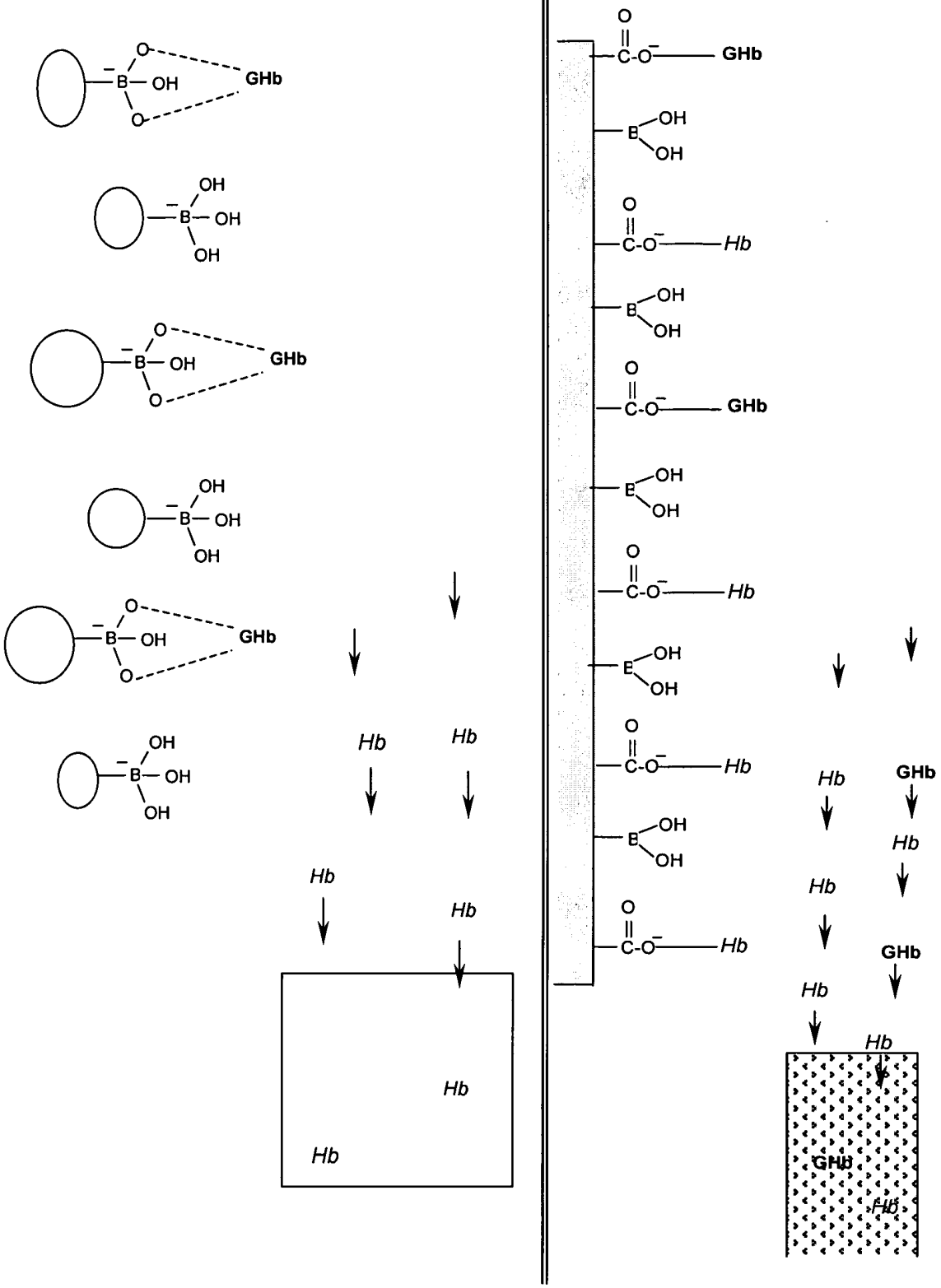


2. Add sample to solid support. Select pH so that positively charged proteins bind to negatively charged groups, leaving both glycated and nonglycated protein bound to support.

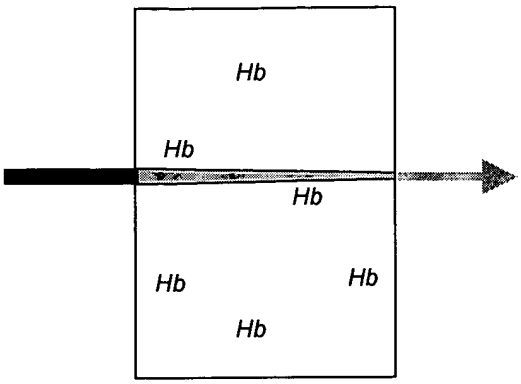


3. Rinse off non-glycated hemoglobin.

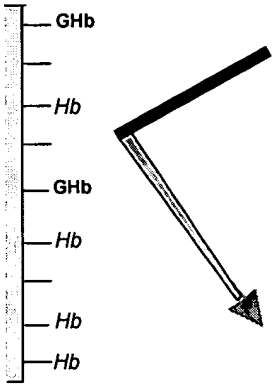
3. [both glycated and non-glycated protein remain on support]



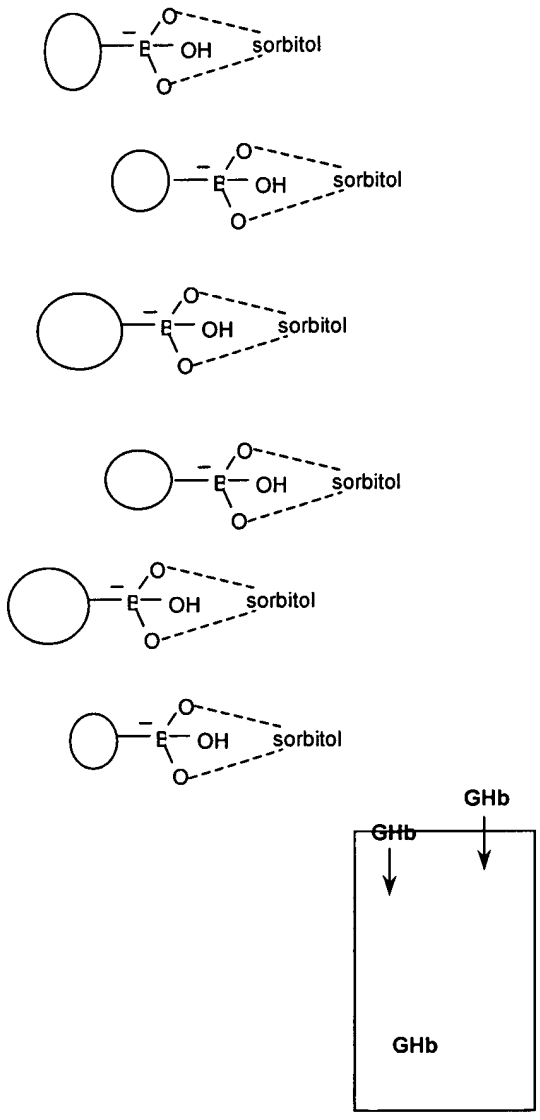
4. Measure absorbance of collected rinse (non-glycated hemoglobin). Not on support.



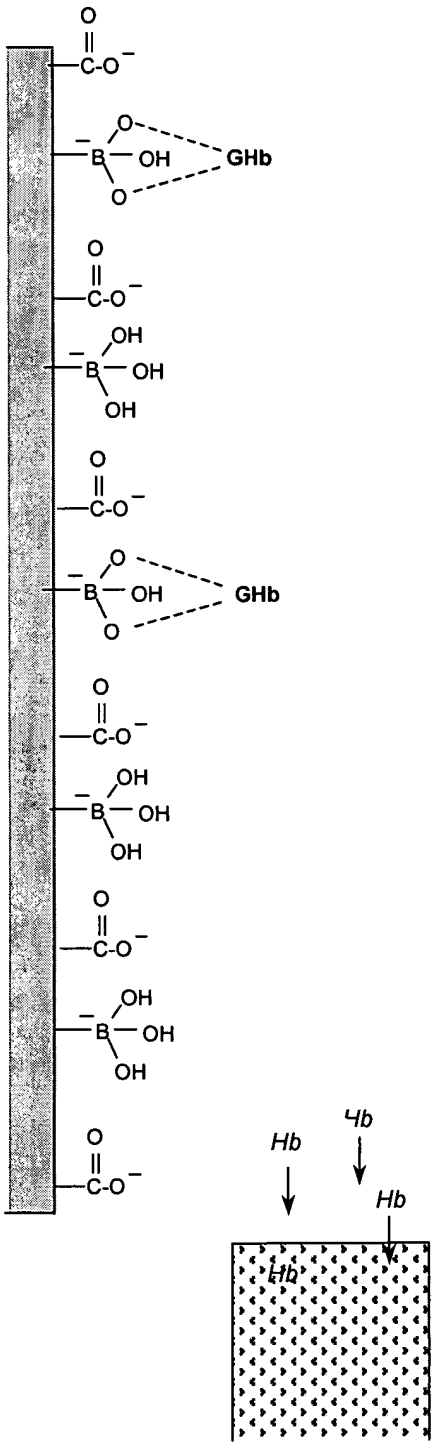
4. Measure total bound protein on solid support (both glycated and non-glycated)



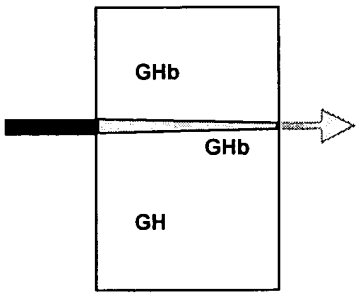
5. Add a buffer and a diol sugar (i.e. sorbitol, glucose, ribose) to desorb glycosylated hemoglobin. Collect GHb.



5. Change pH to remove both nonglycated and glycated protein from the negatively-charged groups. Glycated protein immediately rebinds to boryl groups; non-glycated is removed



6. Measure absorbance of rinsed and collected GHb (liquid phase; not bound on support).



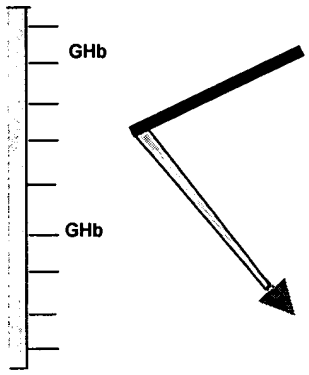
The absorbance of the collected GHb is measured and used to calculate the concentration of glycated hemoglobin.

The percent glycated hemoglobin is calculated as follows:

$$\%GHb = \frac{\text{GHb conc}}{\text{GHb conc + non-glycated Hb conc}}$$

or, in this example: 3/(3+6) = 33.3%

6. Measure the glycated protein bound on the support



The two measurements are used to determine amount or ratio of glycated protein (e.g. hemoglobin) in the sample.

The percent glycated hemoglobin is calculated as follows:

$$\%GHb = \frac{\text{GHb concentration}}{\text{total Hb concentration}}$$

or in this example: 2/6 = 33.3%

Thus, whereas Dean teaches a method for measuring glycated hemoglobin, Dean uses only one buffer and binds the glycated hemoglobin only to boryl groups. Dean also requires separation of the glycated hemoglobin from the non-glycated hemoglobin before any measurement is taken. In the instant application, measurements of both the total protein concentration and the glycated protein concentration are made on the solid support, and may be taken at the same site. Two different pHs are used so that the glycated protein is bound twice on the support: first to the negatively charged carboxy groups (along with the non-glycated protein) and second to the boryl groups. Binding the total protein to negatively charged groups at the same time and then rapidly binding just the glycated protein to boryl groups on the same site

allows the assay to be performed at a single location, and eliminates the need for an incubation period.

3. Sanders does not supply the deficiencies of Dean et al.

Sanders measures glycosylated hemoglobin in solution, not on a solid support. Sanders first removes the nonglycosylated hemoglobin, then measures the amount of glycoslyated hemoglobin in solution. There is no disclosure of measuring bound glycosylated hemoglobin, nor bound nonglycoslyated hemoglobin, nor is there a disclosure of first binding total hemoglobin to a negatively charged group, then changing pH and rebinding only glycosylated hemoglobin to a hydroxyboryl group.

4. May & Richards fail to supply the deficiencies of Dean et al.

May & Richards disclose a lateral flow assay with two distinct binding zones. The first zone binds only glycated hemoglobin. Next, the sample, depleted of glycated hemoglobin, flows to the second zone, where all remaining hemoglobin is bound; however, because the glycated form was already removed by the first zone, "any haemoglobin which is subsequently absorbed in the second binding zone should be the non-glycated fraction." This reference fails to disclose first binding and measuring total protein, then changing the pH to release all protein and re-bind the glycated protein to hydroxyboryl groups without an incubation period. The various binding groups are not interspersed, as required in the claims, but are sequentially laid out on a lateral flow strip, requiring reading of the strip at two separate spatial locations.

There is no suggestion in the art to modify or combine the references as suggested by the PTO. (Indeed, to the extent the PTO relies on inherency, there is even less suggestion, since a person skilled in the art would not be aware of inherent but undisclosed properties.) In particular, the prior art does not disclose any advantage to a support having interspersed hydroxyboryl and negatively charged groups. It does not disclose first binding and measuring total protein using a negatively charged group. It does not disclose changing the pH to release all protein and immediately rebinding the glycated protein to hydroxyboryl groups. It does not disclose measuring the re-bound glycated protein in a second measurement step. Even a hindsight reconstruction of all three references would not result in the claimed method. For these reasons, and all the reasons discussed above, the prior art neither anticipates nor renders obvious the present invention.

CONCLUSION

The Applicants have endeavored to address all of the Examiner's concerns as expressed in the previous Office Actions. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested. In addition, the Applicant suggests that the new claims are all directed to the same patentable invention. However, because the claims have been rewritten, the Examiner is requested to reconsider the application of the previous restriction requirement.

If any issues remain that could be resolved by telephone, the Examiner is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 12-6-05

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